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Effects of Perineural Pregabalin Infusion on Peripheral Neuropathy in Sprague Dawley Rats (rattus norvegicus)

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14. ABSTRACT

Background: Neuropathic pain is a common contributor to chronic pain syndromes in wounded warriors. We seek to answer whether the direct application of pregabalin to an injured nerve would relieve neuropathic pain. Methods: Forty male Sprague Dawley rats were randomized into four study groups: Sciatic nerve crush injury with perineural pregabalin infusion (T), sciatic crush injury with perineural saline infusion (SA), nerve crush injury with subcutaneous pregabalin (SC), and a sham group without nerve injury (C). Results: Group T had significantly better pain behavior scores than both Group SC and Group SA. Pregabalin does not appear to have neurotoxic effects. Conclusions: Perineural pregabalin treatment is superior to systemic pregabalin in reducing pain behavior in a sciatic nerve crush injury model demonstrating that the drug likely has a peripheral mechanism of action in addition to central mechanisms. Perineural application of pregabalin to an injured nerve may be promising as a novel approach for the treatment of neuropathic pain.

15. SUBJECT TERMS

Neuropathic pain, perineural pregablin, analgesia

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Perineural Pregabalin Infusion in a Rat Neuropathic Pain Model

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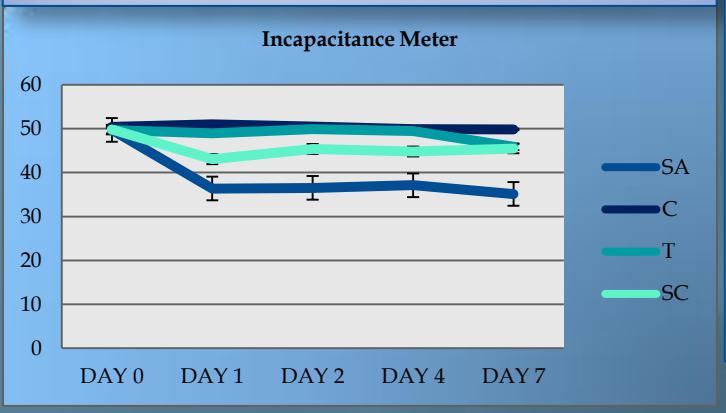
INTRODUCTION

Peripheral neuropathy is a painful condition that has few medications available for its treatment. Pregabalin (Lyrica®) was FDA approved in 1999 for the treatment of epilepsy and has also been used in the treatment of neuropathy. Pregabalin is an orally administered medication that is believed to exert its effect through interaction with the α2δ1 calcium channel subunits in the CNS. Recent data also suggest that pregabalin's antinociceptive effects may be mediated by inhibiting the anterograde trafficking of the α2δ1 calcium channel subunit in the peripheral nervous system.
Hypothesis/Objective: We hypothesize that the perineural application of a solution of pregabalin will improve neuropathic pain and be superior to systemic pregabalin in a rat sciatic nerve injury model.

MATERIALS AND METHODS

Forty male Sprague Dawley rats were randomized into four study groups: Sciatic nerve crush injury with perineural pregabalin infusion (T), sciatic crush injury with perineural saline infusion (SA), nerve crush injury with subcutaneous pregabalin infusion (SC), and a sham group without nerve injury (C). Drug or vehicle was continuously infused via a mini-osmotic pump with either a 1% solution of Pregabalin (Groups T and SC) or Saline (Groups SA, and C) for a period of 7 days. All animals underwent nociceptive behavioral testing using guarding, incapacitance meter, von Frey, and heat lamp tests on post-operative days 1, 2, 4, and 7. On day 7, the sciatic nerves were harvested for either histologic or immunohistochemical testing.



RESULTS

Behavioral Tests: Group T had significantly better guarding scores than groups SC or SA at all post–operative time points ($p<0.01$) and had significantly better incapacitance scores than groups SC and SA on post-operative days 1,2, and 4 ($p<0.01$). Group SC has significantly better guarding and incapacitance scores than group SA at all post-operative time points ($p<0.01$). There was no significant difference between any group at any time point with von Frey or heat lamp testing.

Pathology: All perineural catheter tips were in place at end of study and drug delivery confirmed. Nerve crush injury produced significant axonal degeneration and necrosis with proliferation of Schwann cells and influx of macrophages in all specimens. There was no difference in severity between crush specimens. All injured specimens appeared to be at the same stage of injury progression. All injured nerves appeared normal a short distance proximal to the injury site. Contralateral nerves appeared normal.

CONCLUSIONS

Perineural pregabalin treatment is superior to systemic pregabalin in reducing pain behavior in a sciatic nerve crush injury model demonstrating that the drug likely has a peripheral mechanism of action in addition to central mechanisms. Perineural pregabalin does not appear to inhibit the natural injury/repair course during the first 7 days after crush injury. Perineural application of pregabalin may be promising as a novel approach for the treatment of neuropathic pain